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NEWS 30 Apr 11 Display formats in DGENE enhanced
NEWS 31 Apr 14 MEDLINE Reload
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced
NEWS 33 Jun 13 Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35 Apr 28 RDISCLOSURE now available on STN
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NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB
NEWS 43 Jun 06 PASCAL enhanced with additional data
NEWS 44 Jun 20 2003 edition of the FSTA Thesaurus is now available
NEWS 45 Jun 25 HSDB has been reloaded

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=> s l1 and tet
L2 47 L1 AND TET

=> s l2 and transgen? -
L3 22 L2 AND TRANSGEN?

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L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2003:236446 CAPLUS
DN 139:1619
TI Reengineering Inducible Cardiac-Specific ***Transgenesis*** With an Attenuated Myosin Heavy Chain Promoter
AU Sanbe, Atsushi; Gulick, James; Hanks, Mark C.; Liang, Qiangrong; Osinska, Hanna; Robbins, Jeffrey
CS Dep. Pediatr., Div. Mol. Cardiovasc. Biol., Child. Hosp. Res. Found., Cincinnati, OH, USA
SO Circulation Research (2003), 92(6), 609-616
CODEN: CIRUAL; ISSN: 0009-7330
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Despite the advantages of reversibly altering cardiac ***transgene*** expression, the no. of successful studies with inducible cardiac-specific ***transgene*** expression remains limited. The utility of the current system is hampered by the large no. of lines needed before a nonleaky inducible line is isolated and by the use of a heterologous virus-based minimal promoter in the responder line. We developed an efficient, exptl. flexible system that enables us to reversibly affect both abundant and nonabundant cardiomyocyte proteins. The use of bacterial-codon-based transactivators led to aberrant splicing, whereas other more efficient transactivators, by themselves, caused disease when expressed in the heart. The redesign of the system focused on developing stable transactivator-expressing lines in which expression was driven by the mouse .alpha.-myosin heavy chain promoter. A minimal responder locus was derived from the same promoter, in which the GATA sites and thyroid responsive elements responsible for robust cardiac specific expression were ablated, leading to an attenuated promoter that could be inducibly controlled. In all cases, whether activated or not, expression mimicked that of the parental promoter. By use of this system, an inducible expression of an abundant contractile protein, the atrial isoform of essential myosin light chain 1, and a powerful biol. effector, glycogen synthase kinase-3.beta. (GSK-3.beta.), were obtained. Subsequently, we tested the hypothesis that GSK-3.beta. expression could reverse a preexisting hypertrophy. Inducible expression of GSK-3.beta. could both attenuate a hypertrophic response and partially reverse a pressure-overload-induced hypertrophy. The system appears to be robust and can be used to temporally control high levels of cardiac-specific ***transgene*** expression.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:836498 CAPLUS
DN 138:199500
TI A predictable ligand regulated expression strategy for stably integrated ***transgenes*** in mammalian cells in culture
AU Anastassiadis, Konstantinos; Kim, Jinhyun; Daigle, Nathalie; Sprengel, Rolf; Scholer, Hans R.; Stewart, A. Francis
CS Max-Planck-Institut fur Molekulare Zellbiologie und Genetik MPI-CBG, BIOTEC, TU Dresden, Dresden, 01307, Germany
SO Gene (2002), 298(2), 159-172
CODEN: GENED6; ISSN: 0378-1119
PB Elsevier Science B.V.
DT Journal
LA English
AB Several strategies for regulated stable ***transgene*** expression in mammalian cells have been described. These strategies have different strengths and weaknesses, however they all share a common problem, namely predictability in application. Here we address this problem using the

leading strategy for ligand inducible ***transgene*** expression, the tetracycline repressor system. Initially, we found the best stable clone out of 48 examd. showed only 6-fold inducibility. Hence we looked for addns. and modifications that improve the chances of a successful outcome. We document three important aspects; first, use of a mammalian codon-optimized tetracycline repressor gene; second, addn. of a steroid hormone receptor ligand binding domain to the tetracycline repressor-virion protein 16 fusion protein activator; third, flanking the ***tet*** -operator/ ***transgene*** cassette with insulator elements from the chicken .beta.-globin locus. By inclusion of these three design features, 18/18 clones showed low basal and highly inducible (>50.times.) expression.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2001:851354 CAPLUS
DN 135:370244
TI Over-expression of glycogen synthase kinase-3.beta. in a murine model for neurodegenerative disease
IN Perez, Felix Hernandez; De Grado, Jesus Avila
PA Consejo Superior de Investigaciones Cientificas, Spain; Ruffles, Graham Keith; Lozano, Jose Javier Lucas
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001088109	A2	20011122	WO 2001-GB2218	20010518
WO 2001088109	A3	20020704		
WO 2001088109	C1	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1280404	A2	20030205	EP 2001-936609	20010518

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI GB 2000-12056 A 20000518
WO 2001-GB2218 W 20010518
AB A ***transgenic*** animal in which glycogen synthase kinase-3.beta. (GSK-3.beta.) protein is over-expressed is useful as a model for neurodegenerative disease. Regulation of the system is achieved through the tetracycline-regulated transactivator, a chimeric protein comprises of the ***tet*** -repressor DNA binding domain and the VP16 trans-activation domain. Conditional ***transgenic*** mice overexpressing GSK-3.beta. in the brain during adulthood is thus achieved, while avoiding perinatal lethality due to embryonic ***transgene*** expression. These mice show destabilization of .beta.-catenin and hyperphosphorylation of .tau. protein in hippocampus neurons, the latter resulting in pretangle-like somatodendritic localization of .tau.. Neurons displaying somatodendritic localization of .tau. often show abnormal morphologies and detachment from surrounding neuropil. Reactive astrocytosis and microgliosis were indicative of neuronal stress and death. Thus, in vivo overexpression of GSK-3.beta. results in neurodegeneration and these mice can be used as an animal model to study the relevance of GSK-3.beta. deregulation to the pathogenesis of Alzheimer's disease.

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2001:319911 CAPLUS
DN 134:321592
TI Methods to enhance and confine gene expression in cancer therapy
IN Fung, Yuen Kai; Tang, Anne
PA Research Development Foundation, USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001030799	A1	20010503	WO 2000-US29783	20001027

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-162085P P 19991028
AB The present invention provides a novel approach to gene therapy of restricted areas such as tumors. More specifically the present invention presents a method of controlling the expression of therapeutically useful gene products via tissue specific, tumor specific, and inducible promoters to allow enhanced expression of these genes in tumor cells while reducing the background expression of these genes in nontarget cells. The methods introduced here comprise: (a) placing a gene of interest in a plasmid vector driven by a tissue specific promoter or a heat or light inducible promoter; and (b) modifying this vector by including a tetracycline responsive fusion protein which acts as a transcriptional activator, thus permitting regulation of gene expression by varying the levels of tetracycline; (c) modifying this vector by including DNA sequences that reduce or eliminate expression of genes in unintended cells. Also provided are a set of vectors for both sustained and regulated expression. There are also presented novel vectors for the gene therapy treatment of metastatic breast, ovarian and prostate cancer.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2001:886858 CAPLUS
DN 136:1607
TI Use of a tetracycline-controlled promoter, activator and antisense gene in tissue- specific expression in ***transgenic*** mice
IN Orosz, Charles G.; Xia, Dongyuan; Gordillo, Gayle M.
PA USA
SO U.S. Pat. Appl. Publ., 26 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2001049828	A1	20011206	US 2000-547489	20000412

PRAI US 2000-547489 20000412
AB A method and system for controlling the expression of ***transgene*** products in specific tissues in a ***transgenic*** animal while eliminating background expression of the ***transgene*** products in tissues of the animal is provided. The system is a modified form of the tetracycline-regulated expression system for use in mice. The animals with low background expression of the gene are the offspring of a cross between parental mice carrying different components of the regulatory system. One of the parents carries a foreign gene under control of an inducible promoter. The promoter is induced by a transcription factor activated by ligand binding. The second animal carries two genes: one is an antisense version of the ***transgene*** carried by the other parent. This promoter is down-regulated or repressed by the transcription factor that induces the sense form of the gene. The second gene is the gene for the transcription factor under control of a tissue-specific promoter. In the offspring, low levels of leaky gene expression of the sense gene outside the target tissue are blocked by comparable levels of expression of the antisense gene. In the target tissue the expression of the antisense gene is repressed, allowing expression of the desired gene. In a preferred embodiment, the transactivator regulator is tetracycline and the transactivator protein is the rtTA protein. Administration of a transactivator regulator like tetracycline to a mouse, produced in accordance with the method described above, results in enhanced expression of the exogenous gene and reduced expression of the antisense gene product in target tissues. Accordingly, the mouse can be used for studying the impact of the ***transgene*** product on the biol. of the mouse under defined conditions of expression.

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2001:471732 CAPLUS
DN 136:145744
TI ***Tet*** -system for the regulation of gene expression during embryonic development
AU Fedorov, Lev M.; Tyrsin, Oleg Yu.; Krenn, Veit; Chernigovskaya, Elena V.; Rapp, Ulf R.
CS Institut fur Medizinische Strahlenkunde und Zellforschung, Bayerische Julius-Maximilians-Universitat Wurzburg, Wurzburg, D-97078, Germany
SO Transgenic Research (2001), 10(3), 247-258
CODEN: TRSEES; ISSN: 0962-8819
PB Kluwer Academic Publishers
DT Journal
LA English
AB The ability to control gene expression in a temporal and spatial manner provides a new tool for the study of mammalian gene function particularly during development and oncogenesis. In this study the suitability of the ***tet*** -system for investigating embryogenesis was tested in detail. The tTACMV (M1) and rTACMV -3 (reverse Tc-controlled transactivator) ***transgenic*** mice were bred with NZL-2 bi-reporter mice contg. the vector with a tTA/rTA responsive bidirectional promoter that allows simultaneous regulation of expression of two reporter genes encoding luciferase and .beta.-galactosidase. In both cases reporter genes were found to be expressed in a wide spectrum of tissues of double ***transgenic*** embryos and adult mice. The earliest expression was detected in tTACMV (M1)/NZL-2 embryos at embryonic day 10.5 (E10.5) and rTACMV -3/NZL-2 embryos at E13.5. Doxycycline abolished .beta.-gal expression in tTACMV (M1)/NZL-2 but induced it in rTACMV -3/NZL-2 embryos including late stages of embryogenesis. The tTA and rtTA transactivators thus revealed a partially complementary mode of action during second half of embryonic development. These expts. demonstrated that both ***Tet*** regulatory systems function during embryonic development. We conclude

that the ***Tet*** systems allows regulation of gene expression during embryonic development and that "double reporter" animals like the NZL-2 mice are useful tools for the characterization of newly generated ***tet*** transactivator lines expressing tTA (or rtTA) in embryonic as well as in adult tissues.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2001:909214 CAPLUS
DN 136:364436
TI Modulation of myosin A expression by a newly established tetracycline repressor-based inducible system in Toxoplasma gondii
AU Meissner, Markus; Brecht, Susan; Bujard, Hermann; Soldati, Dominique
CS Zentrum for Molekulare Biologie, Universitat Heidelberg, Heidelberg, 69102, Germany
SO Nucleic Acids Research (2001), 29(22), e115/1-e115/10
CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
AB We have developed a control system for regulating gene activation in Toxoplasma gondii. The elements of this system are derived from the Escherichia coli tetracycline resistance operon, which has been widely used to tightly control gene expression in eukaryotes. The tetracycline repressor (tetR) interferes with transcription initiation while the chimeric transactivator, composed of the tetR fused to the activating domain of VP16 transcriptional factor, allows ***tet*** -dependent transcription. Accordingly, tetracycline derivs. such as anhydrotetracycline, which is well tolerated by T. gondii, can serve as effector mols., allowing control of gene expression in a reversible manner. As a prerequisite to functionally express the tetR in T. gondii, the authors used a synthetic gene with change of codon frequency. Whereas no activation of transcription was achieved using the synthetic tetracycline-controlled transactivator, tTA2s, the TetRs modulates parasite transcription over a range of .apprx.15-fold as measured for several reporter genes. The tetR-dependent induction of the T. gondii myosin A ***transgene*** expression drastically down-regulates the level of endogenous MyoA. This myosin is under the control of a tight feedback mechanism, which occurs at the protein level.
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:520955 CAPLUS
DN 138:67414
TI A regulatory network for the efficient control of ***transgene*** expression
AU Imhof, Markus O.; Chatellard, Philippe; Mermod, Nicolas
CS Laboratory of Molecular Biotechnology, Center for Biotechnology UNIL-EPFL, University of Lausanne, Lausanne, 1015, Switz.
SO Journal of Gene Medicine (2000), 2(2), 107-116
CODEN: JGMEFG; ISSN: 1099-498X
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Expression of heterologous genes in mammalian cells or organisms for therapeutic or exptl. purposes often requires tight control of ***transgene*** expression. Specifically, the following criteria should be met: no background gene activity in the off-state, high gene expression in the on-state, regulated expression over an extended period, and multiple switching between on- and off-states. Here, the authors describe a genetic switch system for controlled ***transgene*** transcription using chimeric repressor and activator proteins functioning in a novel regulatory network. In the off-state, the target ***transgene*** is actively silenced by a chimeric protein consisting of multimerized eukaryotic transcriptional repression domains fused to the DNA-binding tetracycline repressor. In the on-state, the inducer drug doxycycline affects both the derepression of the target gene promoter and activation by the GAL4-VP16 transactivator, which in turn is under the control of an autoregulatory feedback loop. The hallmark of this new system is the efficient ***transgene*** silencing in the off-state, as demonstrated by the tightly controlled expression of the highly cytotoxic diphtheria toxin A gene. Addn. of the inducer drug allows robust activation of ***transgene*** expression. In stably transfected cells, this control is still obsd. after months of repeated cycling between the repressed and activated states of the target genes. This system permits tight long-term regulation when stably introduced into cell lines. The underlying principles of this network system should have general applications in biotechnol. and gene therapy.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:64930 CAPLUS
DN 130:120493
TI A nuclear receptor from Bombyx that act as a transcriptional regulator and its use in the expression of ***transgenes*** in animal cells
IN Gage, Fred H.; Suhr, Steven T.
PA The Salk Institute for Biological Studies, USA
SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9902683	A1	19990121	WO 1998-US14215	19980710
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6300488	B1	20011009	US 1997-891298	19970710
AU 9883895	A1	19990208	AU 1998-83895	19980710
AU 738494	B2	20010920		
EP 998560	A1	20000510	EP 1998-934353	19980710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2002048815	A1	20020425	US 2001-952559	20010913
PRAI US 1997-891298	A2	19970710		
US 1998-91874P	P	19980707		
WO 1998-US14215	W	19980710		

AB A nuclear receptor (bR) of the silk moth Bombyx mori that is useful for the regulation of expression of foreign genes in insect cells is described. BR is thought to be a strong transcriptional regulator in cells of B. mori and it is found to be functional in mammalian cells. Addn. of activation domains to the bR open-reading frame increases the activity of the ligand modulated regulator to afford high-level transcriptional induction. Further modifications to the bR ligand binding domain result in receptors with unique transactivational characteristics. A major advantage of the use of bR is that its natural ligand is not manufd. by mammalian cells, such as diacyl hydrazines, allowing strict control of gene expression using relatively small proteins. A particular example of this is a fusion protein of the receptor, the activation domain of VP16 and the ***tet*** repressor called TTMT (Tebufenozide/Tetracycline Modulated Transactivator) that uses the tetO operator and the ecdysone response element to regulate gene expression by repression (with tetracyclines) and activation by acylhydrazines. Regulation of expression of a reporter gene from a TTMT-responsive promoter by tebufenozide and muristerone A is demonstrated.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:48795 CAPLUS
DN 130:106060
TI ***VP16*** ***fusion*** proteins carrying substitutions in repeats of the the transcription activation domain with different and defined transactivation potentials
IN Baron, Udo; Gossen, Manfred; Bujard, Hermann
PA BASF Aktiengesellschaft, USA
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9901549	A1	19990114	WO 1998-US13993	19980701
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6087166	A	20000711	US 1997-888080	19970703
AU 9881825	A1	19990125	AU 1998-81825	19980701
AU 755417	B2	20021212		
EP 990030	A1	20000405	EP 1998-931801	19980701
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
JP 2002507895	T2	20020312	JP 1999-507457	19980701
US 6271341	B1	20010807	US 2000-577027	20000523
US 2003049842	A1	20030313	US 2001-922568	20010803
PRAI US 1997-888080	A2	19970703		
WO 1998-US13993	W	19980701		
US 2000-577027	A3	20000523		

AB Transcription activating proteins which differ in their transcription activation potential by more than 3 orders of magnitude are described. The transactivators are fusions of a DNA binding protein (e.g., the ***Tet*** repressor tetR) and minimal transcriptional activation domains derived from Herpes simplex virus protein 16 (VP16). Substitution mutations at amino acid position 442 within the minimal VP16 domain provide transactivators with differing transactivation ability. Chimeric activation domains contg. wild type and mutant minimal VP16 domains provide addnl. variants with differing transactivation ability. Various

aspects of the invention pertain to nucleic acid mols., vectors, host cells, fusion proteins, ***transgenic*** and homologous recombinant organisms and methods of regulating gene transcription. A series of fusion proteins of tetR and VP16 transcription activation domain analogs were constructed and tested for their ability to drive expression of a reporter gene in response to tetracyclines. Fusion proteins contg. an inactive analog of the activation peptide showed low levels of induction by tetracycline (.gtoreq.0.03% of a tetR- ***VP16*** ***fusion*** protein control). Fusion proteins contg. an active analog of the activation peptide showed levels of induction up 230% of controls.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:808649 CAPLUS
DN 132:45794
TI Methods for regulation of gene expression using tetO-linked genes controlled by tetR or tetR mutant fusion proteins
IN Bujard, Hermann; Gossen, Manfred
PA BASF A.-G., Germany; Basf Bioresearch Corp.; Knoll A.-G.
SO U.S., 64 pp., Cont.-in-part of U.S. 5,789,156.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 12

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6004941	A	19991221	US 1995-485740	19950607
US 5464758	A	19951107	US 1993-76726	19930614
US 5650298	A	19970722	US 1994-260452	19940614
US 5654168	A	19970805	US 1994-275876	19940715
US 5789156	A	19980804	US 1995-383754	19950203
PRAI US 1993-76327	B2	19930614		
US 1993-76726	A2	19930614		
US 1994-260452	A2	19940614		
US 1994-270637	B2	19940701		
US 1994-275876	A2	19940715		
US 1995-383754	A2	19950203		

AB Nucleic acid mols. and proteins useful for regulating the expression of genes in eukaryotic cells and organisms are disclosed. The invention provides a transcriptional activator fusion protein which binds to ***tet*** operator sequences and stimulates transcription of a ***tet*** operator-linked gene in the presence, but not the absence, of tetracycline (or analog thereof). The invention further provides transcriptional inhibitor fusion proteins which inhibit transcription of a ***tet*** operator-linked gene in a regulated manner. In one embodiment, the inhibitor fusion protein binds to ***tet*** operator sequences in the absence, but not the presence, of tetracycline (or analog). In another embodiment, the inhibitor fusion protein binds to ***tet*** operator sequences in the presence, but not the absence, of tetracycline (or analog). The transcriptional activator and inhibitor fusion proteins of the invention can be used in combination to regulate expression of one or multiple ***tet*** operator-linked genes. Novel ***tet*** operator-contg. transcription units which allow for coordinate or independent tetracycline-regulated expression of two or more genes by the transcriptional modulators of the invention are also disclosed. A gene for a ***tet*** repressor which binds to its target DNA in the presence rather than the absence of tetracycline was prepd. by mutagenesis. This gene was fused to a sequence encoding the C-terminal 130 amino acids of herpes simplex virus VP16 to create a chimeric gene encoding a tetracycline-inducible transactivator. This transactivator was shown to function in HeLa cells and in ***transgenic*** mice. Activation by 3-5 orders of magnitude was obsd. upon addn. of tetracycline (or tetracycline analog). Genes for tetracycline-regulated transcriptional inhibitors comprising TetR fused to a v-erbA or Krueppel silencer domain were also prep. In addn., a combinatorial anal. of amino acid-substituted analogs of the TetR repressor and base-substituted analogs. of the operator was undertaken to find combinations showing the most effective induction or repression.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:392567 CAPLUS
DN 131:40552
TI Mice ***transgenic*** for a tetracycline-inducible transcriptional activator
IN Bujard, Hermann; Gossen, Manfred
PA University of Heidelberg, Germany
SO U.S., 63 pp., Cont.-in-part of U.S. Ser. No. 383,754.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 12

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5912411	A	19990615	US 1995-487472	19950607
US 5464758	A	19951107	US 1993-76726	19930614
US 5650298	A	19970722	US 1994-260452	19940614
US 5654168	A	19970805	US 1994-275876	19940715
US 5789156	A	19980804	US 1995-383754	19950203
US 6242667	B1	20010605	US 1998-161902	19980928
PRAI US 1993-76327	B2	19930614		
US 1993-76726	A2	19930614		
US 1994-260452	A2	19940614		
US 1994-270637	B2	19940701		
US 1994-275876	A2	19940715		
US 1995-383754	A2	19950203		
US 1995-487472	A1	19950607		

AB Nucleic acid mols. and proteins useful for regulating the expression of genes in eukaryotic cells and organisms are disclosed. The invention provides a transcriptional activator fusion protein which binds to ***tet*** operator sequences and stimulates transcription of a ***tet*** operator-linked gene in the presence, but not the absence, of tetracycline (or analog thereof). The invention further provides transcriptional inhibitor fusion proteins which inhibit transcription of a ***tet*** operator-linked gene in a regulated manner. In one embodiment, the inhibitor fusion protein binds to ***tet*** operator sequences in the absence, but not the presence, of tetracycline (or analog). In another embodiment, the inhibitor fusion protein binds to ***tet*** operator sequences in the presence, but not the absence, of tetracycline (or analog). The transcriptional activator and inhibitor fusion proteins of the invention can be used in combination to regulate expression of one of multiple ***tet*** operator-linked genes. Novel ***tet*** operator-contg. transcription units which allow for coordinate or independent tetracycline-regulated expression of two or more genes by the transcriptional modulators of the invention are also disclosed. A gene for a ***tet*** repressor which binds to its target DNA in the presence rather than the absence of tetracycline was prepd. by mutagenesis. This gene was fused to a sequence encoding the C-terminal 130 amino acids of herpes simplex virus VP16 to create a chimeric gene encoding a tetracycline-inducible transactivator. This transactivator was shown to function in HeLa cells and in ***transgenic*** mice. Activation by 3-5 orders of magnitude was obsd. upon addn. of tetracycline (or tetracycline analog). Genes for tetracycline-regulated transcriptional inhibitors comprising TetR fused to a v-erbA or Krueppel silencer domain were also prep. In addn., a combinatorial anal. of amino acid-substituted analogs of the TetR repressor and base-substituted analogs. of the operator was undertaken to find combinations showing the most effective induction or repression.
RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1998:344524 CAPLUS
DN 129:13217
TI Diminishing viral gene expression by promoter replacement in adenoviral vectors
IN Fang, Bingliang; Roth, Jack A.
PA Board of Regents, The University of Texas System, USA; Fang, Bingliang; Roth, Jack A.
SO PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9821350	A1	19980522	WO 1997-US20608	19971112
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9852539	A1	19980603	AU 1998-52539	19971112
US 6110744	A	20000829	US 1997-968014	19971112
PRAI US 1996-30675P	P	19961113		
WO 1997-US20608	W	19971112		

AB The present invention provides viral vectors that have been engineered to contain a synthetic promoter that controls at least one essential gene. The synthetic promoter is induced by a specific gene product not normally produced in the cells in which the viral vector is to be transferred. The vectors are propagated in producer or helper cells that express the inducing factor, thereby permitting the virus to replicate to high titer. The lack of the inducing factor in the target cells precludes viral replication, however, meaning that no vector toxicity or immunogenicity arises. Where the virus carries a gene of interest, this should provide for higher level expression for longer periods of time than with current vectors. Methods for making the vectors, helper cells, and their use in protein prodn., vaccines and gene therapy are disclosed. Thus, the promoter region of adenovirus E4 was replaced with a synthetic promoter composed of a minimal TATA box and five consensus 17-mer5 GAL4-binding site elements (GAL4/TATA). A shuttle vector consisting of the adenovirus type 5 backbone into which a human factor IX ***transgene*** driven by the Rous sarcoma virus-LTR was inserted into the E1 region was used to supply the adenoviral E4 region. Recombinant adenoviruses contg. the RSV promoter-derived human factor IX cDNA and adenovirus E4 gene driven by the GAL4/TATA promoter were constructed by cotransfection of the transfer plasmids with a fragment contg. human factor IX ***transgene*** into producer cells. The resulting recombinant adenoviruses obtained by

homologous recombination, when transduced into non-producer cells, maintain high levels of ***transgene*** expression while at the same time exhibit low levels of adenoviral gene expression. The recombinant adenoviruses exhibit reduced toxicity and attenuated CTL response resulting from E4 inactivation.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1997:465710 CAPLUS
DN 127:171988
TI Tetracycline-controlled transcription in eukaryotes: novel transactivators with graded transactivation potential
AU Baron, Udo; Gossen, Manfred; Bujard, Hermann
CS ZMBH, Heidelberg, 69120, Germany
SO Nucleic Acids Research (1997), 25(14), 2723-2729
CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
AB Several tetracycline-controlled transactivators (tTA) were generated which differ in their activation potential by >3 orders of magnitude. The transactivators are fusions between the ***Tet*** repressor and minimal transcriptional activation domains derived from Herpes simplex virus protein 16 (VP16). By reducing the VP16 moiety of the previously described tTA to 12 amino acids, potential targets for interactions with various cellular transcription factors were eliminated, as were potential epitopes which may elicit a cellular immune response. When compared with the originally described tTA, these new transactivators are tolerated at higher intracellular concns. This will facilitate establishment of ***tet*** regulatory systems under a variety of conditions, but particularly when cell type-restricted tetracycline-controlled gene expression is to be achieved in ***transgenic*** organisms via homologous recombination.

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1997:127494 CAPLUS
DN 126:127877
TI An autoregulatory tetracycline-regulated system for inducible gene expression in eukaryotes
IN Schatz, David G.
PA Yale University, USA; Schatz, David G.
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9640946	A1	19961219	WO 1996-US10109	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
US 5851796	A	19981222	US 1995-474169	19950607
AU 9662745	A1	19961230	AU 1996-62745	19960607
EP 832254	A1	19980401	EP 1996-921541	19960607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11507539	T2	19990706	JP 1996-502206	19960607
PRAI US 1995-474169		19950607		
WO 1996-US10109		19960607		

AB A tetracycline-regulated system which provides autoregulatory, inducible gene expression in cultured cells and ***transgenic*** animals is described. In the autoregulatory plasmid pTet-tTAk, a modified tTA gene called tTAk was placed under the control of Tetp. Tetracycline prevents tTA from binding to Tetp, preventing expression of both tTA and luciferase. This neg. feedback cycle ensures that little or no tTA is produced in the presence of tetracycline, thereby reducing or eliminating possible toxic effects. When tetracycline is removed, however, this strategy predicts that tiny amts. of tTA protein (which may result from the leakiness of the minimal promoter), will bind to ***Tet*** -op and stimulate expression of the tTAk gene. A pos. feedforward loop is initiated which in turn leads to higher levels of expression of tTA and thus, luciferase. Polynucleotide mols. encoding the autoregulatory system, as well as methods of enhancing or decreasing the expression of desired genes, and kits for carrying out these methods are described. The system was demonstrated in NIH3T3 cells and in ***transgenic*** mice. In the ***transgenic*** mice, inducibility, reversibility of the inducibility, and transmission of the ***transgenes*** from founders to progeny was shown.

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:746323 CAPLUS
DN 126:15526
TI Glucose-responsive, insulin-producing ***transgenic*** pancreatic .beta.-cells with proliferation regulated by tetracycline
IN Efrat, Shimon
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9631242	A1	19961010	WO 1996-US4792	19960403
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2217652	AA	19961010	CA 1996-2217652	19960403
AU 9655375	A1	19961023	AU 1996-55375	19960403
AU 720662	B2	20000608		
EP 822834	A1	19980211	EP 1996-912616	19960403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11505411	T2	19990521	JP 1996-530530	19960403
US 6114599	A	20000905	US 1998-44297	19980319
US 6242254	B1	20010605	US 2000-492905	20000127
PRAI US 1995-418416	A	19950407		
WO 1996-US4792	W	19960403		
US 1998-44297	A1	19980319		

AB Glucose-regulated insulin producing pancreatic .beta.-cells whose proliferation is controlled by tetracyclines are described for use in the treatment of diabetes. Proliferation is controlled by a fusion protein of the tetracycline repressor tetR and VP16 to regulate expression of an SV40 T antigen gene under control of a ***tet*** operator. The gene for the fusion protein is under control an insulin-responsive promoter. An animal carrying both constructs is prepd. by crossing animals transformed with one of the constructs and .beta.-cells carrying the both constructs are selected in vitro. The construction of these cells in mice is demonstrated.

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1997:51843 CAPLUS
DN 126:100260
TI Fusion proteins of the tetracycline repressor for use in tetracycline regulation of gene expression in eukaryotes
IN Bujard, Hermann; Gossen, Manfred; Hillen, Wolfgang; Helbl, Vera; Schnappinger, Dirk
PA BASF A.-G., Germany; Knoll Aktiengesellschaft
SO U.S., 62 pp., Cont.-in-part of U.S. Ser. No. 383,754.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 12

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5589362	A	19961231	US 1995-485971	19950607
US 5464758	A	19951107	US 1993-76726	19930614
US 5650298	A	19970722	US 1994-260452	19940614
US 5654168	A	19970805	US 1994-275876	19940715
US 5789156	A	19980804	US 1995-383754	19950203
WO 9640892	A1	19961219	WO 1996-US9049	19960606
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRAI US 1993-76327	B2	19930614		
US 1993-76726	A2	19930614		
US 1994-260452	A2	19940614		
US 1994-270637	B2	19940701		
US 1994-275876	A2	19940715		
US 1995-383754	A2	19950203		
US 1995-485971	A	19950607		

AB Fusion proteins of amino acid-substituted ***tet*** repressors and transcription factors that bind class B ***tet*** operators that can be used in tetracycline regulation of expression of foreign genes in eukaryotes. Genes encoding these proteins are also described. The ***tet*** operators also have nucleotide substitutions in one or two of the 3'-bases (+4 or +6). A pool of multiply mutant ***tet*** repressor genes was generated by bisulfite mutagenesis of the tetR gene and mutants with a reverse regulation phenotype (induction of gene expression by tetracyclines rather than repression) were identified using a galK/lacZ/ ***tet*** operator reporter system. Fusion proteins of the N-terminal regions of these proteins and herpes simplex VP16 were prepd. by std. methods. Their efficacy was tested in a reporter gene system using the CMV promoter and a heptameric ***tet*** operator to regulate expression of a luciferase reporter in HR-5 cells. Doxycycline induced gene expression by 237-1660-fold and two genes under the control of ***tet*** operators could be induced coordinately. Fusion proteins of silencer domains, e.g. Krueppel or v-erbA proteins, are described for use as repressors. A combinatorial anal. of amino acid-substituted analogs of the repressor and base-substituted analogs of the operator was undertaken to find combinations showing the most effective induction or repression.

L4 ANSWER 18 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
INC.DUPLICATE
1
AN 1996:316328 BIOSIS

DN PREV199699038684
TI Rapid retroviral delivery of tetracycline-inducible genes in a single autoregulatory cassette.
AU Hofmann, Andreas; Nolan, Garry P.; Blau, Helen M. (1)
CS (1) Dep. Mol. Pharmacol., Stanford Univ. Sch. Med., Stanford, CA 94305-5332 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (1996) Vol. 93, No. 11, pp. 5185-5190. ISSN: 0027-8424.
DT Article
LA English
AB We describe a single autoregulatory cassette that allows reversible induction of ***transgene*** expression in response to tetracycline (***tet***). This cassette contains all of the necessary components previously described by others on two separate plasmids that are introduced sequentially over a period of months (Gossen, M. & Bujard, H. (1992) Proc. Natl. Acad. Sci. USA 89, 5547-5551). The cassette is introduced using a retrovirus, allowing transfer into cell types that are difficult to transfect. Thus, populations of thousands of cells, rather than a few clones, can be isolated and characterized within weeks. To avoid potential interference of the strong retroviral long terminal repeat enhancer and promoter elements with the function of the ***tet*** -regulated cytomegalovirus minimal promoter, the vector is self-inactivating, eliminating transcription from the long terminal repeat after infection of target cells. Tandem ***tet*** operator sequences and the cytomegalovirus minimal promoter drive expression of a bicistronic mRNA, leading to transcription of the gene of interest (lacZ) and the internal ribosome entry site controlled transactivator (***Tet*** repressor- ***VP16*** ***fusion*** protein). In the absence of ***tet*** , there is a progressive increase in transactivator by means of an autoregulatory loop, whereas in the presence of ***tet*** , gene expression is prevented. Northern blot, biochemical, and single cell analyses have all shown that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. Thus, the current cassette of the retroviral construct (SIN-RetroTet vector) allows rapid delivery of inducible genes and should have broad applications to cultured cells, ***transgenic*** animals, and gene therapy.

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:622324 CAPLUS
DN 125:266875
TI Temporal control of the Cre recombinase in ***transgenic*** mice by a tetracycline responsive promoter
AU St-Onge, Luc; Furth, Priscilla A.; Gruss, Peter
CS Dep. Molecular Cell Bio., Max-Planck-Inst. Biophys. Chem., Goettingen, 37018, Germany
SO Nucleic Acids Research (1996), 24(19), 3875-3877 CODEN: NARHAD; ISSN: 0305-1048
PB Oxford University Press
DT Journal
LA English
AB Gene-targeted mice derived from embryonic stem cells are a useful tool to study gene function during development. However, if the mutation is embryonic lethal and the gene is deleted from the onset of development, later functions in adult animals cannot be studied. Recently, the bacterial Cre-loxP site-specific recombination system has successfully been used in ***transgenic*** animals to produce tissue-specific and temporal deletions [Tu et al. (1993) Cell, 73, 1155-1164; Gu et al. (1994) Science, 265, 103-106; Kuehn et al. (1995) Science, 269, 14237-1429]. We have evaluated the tetracycline responsive binary system [Gossen and Bujard (1992) Proc. Natl. Acad. Sci. USA, 89, 5547-5551] for its ability to transiently express the Cre recombinase in ***transgenic*** mice. In this system, a transactivator fusion protein composed of the tetracycline repressor (tetR) and the acidic domain of the herpes simplex viral protein 16 (VP16) can regulate the expression of the Cre gene from a promoter contg. ***tet*** -operator (tetO) sequences. In the absence of tetracycline, the Cre gene is expressed and will induce site-specific recombination between two loxP sites. In the presence of tetracycline, the Cre gene will not be expressed and recombination will not occur.

L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1995:510528 CAPLUS
DN 122:262575
TI Conditional transformation of a pancreatic .beta.-cell line derived from ***transgenic*** mice expressing a tetracycline-regulated oncogene
AU Efrat, Shimon; Fusco-DeMane, David; Lemberg, Hadas; Emran, Obaidullah Al; Wang, Xiaorong
CS Dep. of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(8), 3576-80 CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Conditional oncogene expression in ***transgenic*** mice is of interest for studying the oncoprotein requirements during tumorigenesis and for deriving cell lines that can be induced to undergo growth arrest and enhance their differentiated functions. We utilized the bacterial tetracycline (***Tet***)-resistance operon regulatory system (***tet***) from Tn10 of Escherichia coli to control simian virus 40 (SV40) large tumor (T) antigen (TAg) gene expression and to generate conditionally transformed pancreatic .beta. cells in ***transgenic*** mice. A fusion protein contg. the ***tet*** repressor (tetR) and the activating domain fo the herpes simplex virus protein VP16, which converts the repressor into a transcription activator, was produced in .beta. cells of ***transgenic*** mice under control of the insulin promoter. In a sep. lineage of ***transgenic*** mice, the TAg gene was introduced under control of a tandem array of ***tet*** operator sequences and a minimal promoter, which by itself is not sufficient for gene expression. Mice from the two lineages were then crossed to generate double-***transgenic*** mice. Expression of the tetR fusion protein in .beta. cells activated TAg transcription, resulting in the development of .beta.-cell tumors. Tumors arising in the absence of ***Tet*** were cultured to derive a stable .beta.-cell line. Cell incubation in the presence of ***Tet*** led to inhibition of proliferation, as shown by decreased BrdUrd and [3H]thymidine incorporation. The ***Tet*** deriv. anhydrotetracycline showed a 100-fold stronger inhibition compared with ***Tet*** . When administered in vivo, ***Tet*** efficiently inhibited .beta.-cell proliferation. These findings indicate that transformed .beta. cells selected for growth during a tumorigenesis process in vivo maintain a dependence on the continuous presence of the TAg oncoprotein for their proliferation. This system provides an approach for generation of .beta.-cell lines for cell therapy of diabetes as well as conditionally transformed cell lines from other cell types of interest.

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COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		73.78	73.99

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) TOTAL	ENTRY	SINCE FILE SESSION	
CA SUBSCRIBER PRICE		-12.37	-12.37

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